Left Ventricle Systolic Dysfunction, Total Mortality, and Sudden Death in Patients With Myocardial Infarction Treated With N-3 Polynsaturated Fatty Acids

Alessandro Macchia, Aldo Pietro Maggioni, Maria Grazia Franzosi, Luigi Tavazzi, Gianni Tognoni, Francesca Valgussa, Roberto Marchioli, The GISSI Prevenzione Investigators, Consorzio Mario Negri Sud, Santa Maria Imbola, Italy

Background: Severe left ventricular systolic dysfunction (LVSD) after myocardial infarction (MI) increases the risk of heart failure, mortality (M) and sudden death (SD). Several treatments reduce M and SD in this cohort. Less information is available on the association between mild/moderate LVSD, M and particularly SD. N-3 polynsaturated fatty acids (n-3) reduce M and SD in post-MI, but the effect in patient with LVSD is unknown.

Methods: We selected 9351 post-MI patients from the GISSI-Prevenzione trial who had a measurement of ejection fraction (EF). LVSD was classified as absent, EF >50%; mild, EF 46-50%; moderate, EF 41-45%; severe, EF <40%. Cox regression models adjusted for prognostic indicators were fitted.

Results: As compared with patients without LVSD, the 46% with LVSD had higher rates of M and SD (12.3% vs 5.8% and 3.4% vs 1.3%). There was a graded association between LVSD, M and SD. Treatment with n-3 reduced M as well as SD in patients with and without LVSD (heterogeneity test NS). When we assessed the effect of n-3 on SD according to the grade of LVSD, the test for trend was statistically significant thus indicating a concentrated effect of n-3 in patients with progressively worsening of LV systolic function.

Conclusions: mild/moderate LVSD is a common feature of post-MI patients and is associated with increased risk of M and SD. Treatment with n-3 decreased M and SD in patients with and without LVSD. Progressively increasing LVSD is associated with elevated risk of SD and with increased benefit from n-3 perhexiline.

Augmentation of Glucose Metabolism With Perhexiline Improves Maximal Oxygen Consumption and Quality of Life in Patients With Nonischaemic Dilated Cardiomyopathy

Leong Lee, Ross Campbell, Rachel Field, Prasad Gunarawan, Justin Taylor, Matthias Schoen, John Horowitz, Michael Frenneaux, Wales Heart Research Institute, Cardiff, United Kingdom

Background: Despite considerable advances in pharmacotherapy, chronic heart failure (CHF) remains a major cause of morbidity and mortality. Additional effective therapies are needed. Glucose metabolism is more oxygen efficient than free fatty acids (FFA) metabolism at generating ATP. CHF leads to a shift in mitochondrial substrate use from FFA to glucose but whether this represents an adaptive or maladaptive process is unclear. The anti-anginal drug perhexiline further augments glucose metabolism by inhibiting mitochondrial FFA uptake. We hypothesize that augmentation of glucose metabolism is beneficial in CHF and associated with an improvement in symptoms, and peak exercise oxygen consumption (VO2 max), an important measure of both prognosis and functional status.

Methods: This was a randomised double blind placebo controlled trial. 24 patients with Dilated Cardiomyopathy, angiographically normal coronary arteries, and optimally medicated CHF (NYHA III-IV, EF<40%) were randomised to perhexiline (n=12) or placebo (n=12) for 2 months. Cardiopulmonary exercise testing with respiratory gas analysis and completion of the Minnesota Living with Heart Failure Questionnaire (MLHFAQ) were performed before and after treatment.

Results: As expressed as mean ± SEM. VO2max was similar at baseline in the perhexiline and placebo groups (17.1 ± 1.1 vs. 16.0 ± 1.3 ml/kg/min). Following treatment, VO2max was unchanged in the placebo group (16.1 ± 1.5 ml/kg/min) but increased in the perhexiline group (19.6 ± 1.5 ml/kg/min). ANCOVA using baseline values as covariates demonstrated a significant effect of perhexiline vs. placebo on VO2max; p=0.03. MLHFAQ scores were similar at baseline in the perhexine and placebo groups (45.4 ± 7.9 vs. 47.2 ± 6.5 respectively) and fell markedly following treatment in the perhexine group (30.7 ± 6.9) but not in the placebo group (42.8 ± 6.5); ANCOVA, p=0.03.

Conclusions: Treatment with perhexiline leads to an improvement in VO2max and quality of life in Dilated Cardiomyopathy. This benefit suggests that augmentation of glucose metabolism could be beneficial in heart failure even in the absence of underlying ischaemia and represents a potential future treatment strategy.

Improved Myocardial High-Energy Phosphate Metabolism Induces by Partial Free Fatty Acid Inhibition in Patients With Heart Failure

Gabriele Fragasso, Francesco De Cobelli, Gianluca Perseghin, Antonio Esposito, Alin Pallossi, Giorgio Bassanelli, Chiara Montano, Alessandro Del Maschio, Alberto Margonato, Istituto Scientifico/Universita San Raffaele, Milano, Italy

Background: The addition of the partial free fatty acid inhibitor trimetazidine to standard treatment, has been shown to effectively improve left ventricular function in patients (pts) with heart failure. The beneficial effect of trimetazidine has been attributed to preservation of cardiac phosphocreatine (PCr) and adenosine triphosphate (ATP) intracellular levels. Aim of this study was to assess the effects of trimetazidine on PCr and ATP concentrations in pts with heart failure.

Methods: Twelve pts (1 female) with heart failure (6 post-ischemic, 5 hypertensive, 1 dilated cardiomyopathy) on conventional therapy were randomised in a double blind, cross-over study to placebo or trimetazidine (20mg t.i.d) for 90 days. At the end of 90 days, all pts underwent exercise testing, 2D-echocardiography and cine aortic pigtail cannula.

Results: As compared with patients without LVSD, the 46% with LVSD had higher rates of M and SD (12.3% vs 5.8% and 3.4% vs 1.3%). There was a graded association between LVSD, M and SD. Treatment with n-3 reduced M as well as SD in patients with and without LVSD (heterogeneity test NS). When we assessed the effect of n-3 on SD according to the grade of LVSD, the test for trend was statistically significant thus indicating a concentrated effect of n-3 in patients with progressively worsening of LV systolic function.

Conclusions: mild/moderate LVSD is a common feature of post-MI patients and is associated with increased risk of M and SD. Treatment with n-3 decreased M and SD in patients with and without LVSD. Progressively increasing LVSD is associated with elevated risk of SD and with increased benefit from n-3 perhexiline.

Cancer Cardiomyopathy System: Hemodynamic and Renal Effects

Michael R. Zile, Ron Oren, Adrian Van Bakel, Paul Mohacsi, Michael Bohn, Bernd Hammer, Sinisa Gradinac, Jerzy Sadowski, Krzysztof Bartus, Andre Wasler, Marvin A. Konstam, Medical University of South Carolina, Charleston, SC

Background: The purpose of this study was to examine the hemodynamic effects of the Cancer Cardiomyopathy System (CRS), a novel extracorporeal device that superimposes continuous aortic flow on existing pulsatile flow. We hypothesized that by reducing LV afterload and increasing aortic flow the CRS would improve the hemodynamics in patients with acutely decompensated chronic heart failure who were refractory to standard medical therapy. Methods: The inflow to the CRS centrifugal pump was via a percutaneously placed femoral arterial cannula and outflow was via either a graft cannula anastomosed to the left auxiliary artery (n=4) or percutaneously through the femoral artery (n=3) via an aortic pigtail cannula. Results: Seven patients were placed on the CRS and supported for an average of 66 hours (24 hrs to 5 days) with pump flows between 1.2 and 1.5 mls/kg/min. Hemodynamic data are shown in the Figure. Data during and after CRS suggest that the PCWP vs CI relationship is reset. Conclusions: The Cancer CRS, a novel form of cardiac assistance, acting through a low-flow, continuous aortic flow loop, markedly improved PCWP. CI and renal function in patients with refractory heart failure. Hemodynamic and renal functional improvement persisted following discontinuation of the CRS. These results suggest that the CRS may be an effective treatment for decompensated chronic heart failure.